NHS Highly Specialised Services for Rare Mitochondrial Disorders

Full clinical guidelines:

Constipation in Children with Mitochondrial Disease

For quick reference guideline visit:

http://www.mitochondrialdisease.nhs.uk/professional-area/care-guidelines

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Contents

Introduction

Mitochondrial disease is the most commonly inherited neurometabolic disorder of childhood in the UK[1] causing significant morbidity. The phenotype exhibited by children with mitochondrial disease is vast, and multisystem disease is not uncommon. Involvement of the gastrointestinal system is not uncommon, but may be overlooked before formal diagnosis. Mitochondrial diseases defined by a gastrointestinal phenotype such as mitochondrial neurogastronintestinal encephalomyopathy (MNGIE) are rare, as are other well-recognised syndromes in childhood. Constipation is common in children with mitochondrial disorders, and pseudo-obstruction may also be seen. Patients harbouring the m.3243A>G mtDNA mutation in the *MTTL-1* gene appear to be more commonly affected by gastrointestinal dysmotility compared to other genotypes. However, there may be several contributory factors to a child with mitochondrial disease and constipation including reduced mobility and poor exercise tolerance, limited fluid intake, poor diet, concurrent pharmacological agents, and psychological or behavioural difficulties.

Constipation in children with mitochondrial disease is treatable, yet no current guidelines exist for the management of bowel dysmotility in children with this condition. Children should be screened for constipation, or the factors that may contribute to constipation, at the point of diagnosis and serially when reviewed; treatment is more effective when initiated early in the disease course.

Patient-centred Care

This guideline offers expert consensus advice on the management of children with mitochondrial disease, in conjunction with current NICE Guidelines for Constipation in Children. Management of these children should take into account the needs of the child first and foremost, as well as the preferences of the family caring for the affected child. Appropriate information should be given to the child, and their family, in order to involve them in decision-making about their care.

Effective communication between the child, family, primary care physician, secondary care paediatrician, tertiary paediatric gastroenterologist (if involved) and specialist mitochondrial centre is essential. Treatment and care should be supported by the best available information.

Key Priorities for Implementation

Given the broad spectrum of phenotypes in children with mitochondrial diseases, we recommend that gastrointestinal assessment is performed at diagnosis, and serially thereafter during clinical reviews. This should include clinical history and examination, utilization of the Bristol Stool Scale, and further investigations as deemed appropriate.

Specialist opinion should be sought from a Paediatric Gastroenterologist, in conjunction with a Mitochondrial Specialist, if symptoms are recurrent or difficult to treat.

This document is intended for guidance only, and should not replace patient-specific management plans influenced by other factors.

Constipation is the condition in which there is difficulty emptying the bowels, resulting in infrequent bowel movements or stool which is hard.

In maintaining a healthy bowel, children should open their bowels daily passing a soft but formed stool. Children with mitochondrial disease may fail to report constipation unless specifically asked. The Bristol Stool Scale should be used whenever possible to assess stool consistency.

Commonly reported symptoms of constipation in children include early satiety or loss of appetite, abdominal discomfort and/or bloating, behavioural changes and/or sleep disturbance. Overflow diarrhoea secondary to constipation is also a common feature but maybe mistaken for primary diarrhoea.

1. **Diet & lifestyle**

   We should aim to educate children and families about the importance of good bowel hygiene aiming for the passage of a formed soft stool at least once daily. Good hydration is advised in children with mitochondrial disease, ensuring that other co-morbidities (e.g. cardiac or renal disease) have been taken into account. An adequate daily fluid intake, ideally water, appropriate for age and body-weight should be advised.

   Advice on healthy eating and well balanced diets is advocated. Those children with constipation will require additional nutritional advice. Bulk-forming drugs or diet may worsen constipation in mitochondrial disease, possibly due to weakened peristalsis, and thorough dietary

history is advised. Consideration to involve a paediatric dietician, ideally with experience in mitochondrial disease, should be given at an early stage. Consideration of a balanced, low-fibre diet should be given, which must also allow adequate calorific and nutritional content for growth and to combat fatigue associated with mitochondrial dysfunction.

Immobility can contribute to constipation therefore regular physical activity (or changes in posture and positioning for those with severe physical disability) is recommended. Input from a specialist paediatric physiotherapist is advised. This is particularly important during intercurrent illnesses and hospital admissions.

It is good practice to review other pharmacological agents prescribed for the child with mitochondrial disease as numerous medications have constipation as an associated side-effect; risk/benefit and alternatives should be considered by the mitochondrial specialist and the paediatrician who prescribed the drugs initially, in association with the child and their parent / carer.

2. **Investigations**

If screening for *hypothyroidism* did not occur as part of the initial investigation of the child with mitochondrial disease then it should occur to exclude this as a contributory factor for constipation. Coeliac disease is not known to be associated with mitochondrial disease, but is recognised as a cause of constipation in children and therefore a coeliac screen should be considered. Other contributory

causes, such as electrolyte imbalances, should be considered and a low threshold for blood screening given.

Idiopathic constipation does not need to be investigated with abdominal X-rays, ultrasound, transit studies or endoscopy. However, consideration should be given for AXR in children with mitochondrial disease displaying gastroenterological symptoms. Some patients may exhibit chronic dilatation of both the small and large bowel; knowledge of this from AXR may prevent unnecessary surgical intervention at a later date.

3. **Laxative maintenance therapy**

A focused clinical history should identify contributory factors in the child with constipation; these should be addressed accordingly. Maintenance laxative therapy should only be commenced once faecal impaction has be excluded and managed appropriately (see below).

Macrogol agents are preferential first-line therapy in constipation. Paediatric polyethylene glycol 3350+electrolytes maintenance should be started according to age (and if previous disimpaction has occurred); usual daily dosage is ½ - 4 sachets. The dose of polyethylene glycol 3350+electrolytes should be adjusted according to response, aiming for the daily passage of soft, formed stools. Children and parents / carers should be educated about the use of macrogol agents and when to adjust the dosage. If polyethylene glycol 3350+electrolytes is not tolerated then a stimulant laxative such as sodium picosulphate or senna should be commenced;

docusate should be added if stools are hard. Children should be reassessed to ensure impaction has not (re)occurred. Medication should not be stopped abruptly**.**

Most children with constipation due to mitochondrial disease will require laxative therapy throughout childhood and possibly into adult life given the potential underlying smooth muscle involvement and weak peristalsis.

It is advisable to seek an opinion from a Paediatric Gastroenterologist in cases of intractable constipation despite optimum diet, lifestyle and maintenance laxative therapy.

4. **Faecal impaction**

Faecal impaction (severe constipation) may present as 'overflow diarrhoea' and needs urgent management to avoid further complications. Children with mitochondrial disease presenting with pseudo-obstruction should be assessed for faecal impaction and managed appropriately (see below).

Disimpaction regime

Children presenting with faecal impaction require disimpaction. This is ideally managed using macrogol agents at an age-appropriate regime, in the first instance. For children aged <1yr: Paediatric polyethylene glycol 3350+electrolytes ½ sachet/day increasing to 1 sachet/day should be given. For child aged 1-5yrs: Paediatric

polyethylene glycol 3350+electrolytes 2 sachets/day increasing in steps of 2 sachets every 2 days up to a maximum of 8 sachets daily. For children aged 5-12yrs: Paediatric polyethylene glycol 3350+electrolytes 4 sachets/day increasing in steps of 2 sachets/day up to a maximum of 12 sachets daily.

The aim is to pass solid stools initially progressing to loose then watery stools; once watery stools have been passed, maintenance therapy can commence (assuming solid stools were passed first).

5. **Surgical management**

Surgical intervention is rarely required in children with mitochondrial disease and constipation. Rectal biopsy is not required unless there are clinical features of Hirschsprung's disease (i.e. abdominal swelling / bloating, difficulty gaining weight, vomiting). Manual evacuation of the bowel under general anaesthesia should not be performed unless optimum treatment with enteral laxative medication (+/- rectal medication) where appropriate has failed and the child has symptomatic constipation. Discussion with a Paediatric Anaesthetist and consideration as to appropriate anaesthesia will be required if manual evacuation is planned. Close monitoring of serum glucose and electrolytes will be required. Fasting should be avoided; IV fluids should be commenced early. We recommend reference to our Peri-operative Care in Children with Mitochondrial Disease guideline.

An antegrade colonic enema (ACE) procedure is not advised in children with mitochondrial disorders (and metabolic disorders in

general) due to a lack of evidence supporting efficacy of this procedure in children with this condition.

Children with intractable constipation despite optimum management should be referred to a Paediatric Gastroenterologist.

6. **Complications**

Urinary retention, or incomplete urinary voiding, can occur in children with severe constipation and should be sought from history and on clinical examination. Ultrasound of the kidneys, ureters and bladder should be considered if urinary retention is suspected clinically. Adults with advanced m.3243A>G multi-system disease can develop painless urinary retention; there may be associated hydroureter or hydronephrosis. Some children may develop urinary tract infections as a consequence of chronic constipation and should be treated promptly. Urinary microscopy and culture should be performed in constipated children with mitochondrial disease if they present unwell, febrile, vomiting or with abdominal pain.

Upper or lower GI obstruction can occur in children with mitochondrial disease and needs urgent management.

7. **If a child presents acutely with signs of mechanical obstruction**

Acute gastroparesis (e.g. pseudo-obstruction) may occur in isolation or more commonly during an intercurrent illness or following a surgical procedure. This is most commonly recognised in children

harbouring the m.3243A>G mtDNA mutation. They may present vomiting with a distended abdomen. Prompt recognition of potential pseudo-obstruction is crucial in order to initiate appropriate management early. Educating children and families that this is a possible disease complication is advisable.

Keep the child nil by mouth and commence IV fluids (0.9% saline + 5% glucose) and pass a nasogastric tube. A plain abdominal X-ray should be performed. Consider passing a flatus tube if colonic dilatation extends to the rectum. Serum glucose, electrolytes and lactate should be checked on presentation and regularly thereafter. TPN should be considered early if prolonged fasting is likely, and this should be tailored specifically to the childs nutritional and metabolic needs.

There is no evidence for the administration of gastrograffin in children with mitochondrial disease and pseudo-obstruction but it is used in adults patients for both diagnostic and therapeutic purposes (excluding mechanical intestinal obstruction and treating pseudo-obstruction). Surgery is rarely required but it may be good practice to involve the Paediatric Surgery team in case input is required. Early advice from a Paediatric Gastroenterologist should be sought.

Faecal impaction may also be evident and should be treated accordingly (see above).

Notes on the scope of this guidance

This guideline was developed by paediatricians with expertise in mitochondrial diseases from the NHS Highly Specialised Services for Rare Mitochondrial Diseases in the UK (London, Newcastle, Oxford).

Audience

These guidelines are intended for use by:

- healthcare professionals working with children with mitochondrial diseases
- commissioning organizations
- service providers

Guideline Limitations

We acknowledge that there are limitations to these guidelines including:

- lacking a firm evidence base for reference
    - consensus expert opinion is used in conjunction with NICE guidance
- the need for further research (see research recommendations below)

Implementation

Children with mitochondrial disease should have access to a specialist mitochondrial service. Specialist mitochondrial clinics are provided by selected centres in the England (Newcastle, Oxford and London) with the support from NHSE Highly Specialised Services commissioners. Clinical and research experience within these centre, along with access to multi-disciplinary team input is designed to offer the best available care for children with mitochondrial diseases.

We aim to educate patients and parents / carers about mitochondrial disease, along with an understanding of potential gastrointestinal problems and good bowel hygiene to prevent future complications.

Accessing a specialist mitochondrial clinic facilitates the identification of potentially affected family members, or other formal diagnoses to those already exhibiting symptoms.

Care should continue with the local Paediatric service and close liaison is required between the family, local team and mitochondrial service. We recommend local paediatric gastroenterology care for those children with constipation, or other gastroenterological associations with mitochondrial disease, and access to emergency care if required.

Research Recommendations

Natural history studies

Analysis of large cohorts of children with mitochondrial diseases of different genotypes and phenotypes is required to document the effects of constipation on morbidity. The MRC MitoCohort UK offers a unique resource in order to do this.

Pharmacological agents and dietary supplements

Further research involving randomized controlled trials of pharmacological agents and/or dietary supplements for the treatment of constipation in children with mitochondrial disease is required.

Modified diets

The use of modified diets in children with mitochondrial disease and constipation has not been researched. Similar clinical studies in adults are inconclusive to date.

Updating the guidelines

The NHS Highly Specialised Services for Rare Mitochondrial Diseases paediatric guidelines are updated when important new information is available. We check for new evidence annually after publication. If important new evidence is published at other times, we may update the guideline prior to any scheduled changes.

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